REMARKS

The present Amendment is responsive to the Office Action mailed August 7, 2007. Applicant submits concurrently herewith: 1) a Petition for Extension of Time; and 2) a Request for Continued Examination (RCE) Form.

Claims 1-19 are pending in the application. In the Office Action, claims 1-19 have been rejected. In the instant Amendment, claim 4 has been canceled, and claims 1, 6-9 and 11-12 have been amended.

Claim 1 has been amended to incorporate the recitation of claim 4. Claim 11 has been amended similarly. Claims 1 and 11 have also been amended to recite that the particulate carrier material is inert, support for which is set forth in paragraph [0027], for example.

Claims 6-9 and 12 have been amended to delete the recitation "derivative," and replace it with the recitation "salt, solvate or salt solvate." Support for the amendment is found in the specification, *e.g.*, in page 8, paragraph [0028].

No new matter has been added by these amendments. Accordingly entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 6-9, 12 and 14-15 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on the ground that the recitation of "derivative" is unclear. Applicant has amended claims 6-9 and 12 to delete the recitation of "derivative." The rejection is therefore obviated.

THE REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1-19 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Trofast, *et al.*, U.S. Patent 6,030,604 (hereinafter "*Trofast*") in view of Ward *et al.*, U.S. Patent 6,616,914 (hereinafter "*Ward*") and Keller, *et al.*, WO 00/28979 using U.S. Patent 6,645,466 as the English language equivalent (hereinafter "*Keller*"). The Examiner contends that although *Trofast* does not teach carrier particles having a volume median diameter from about 50 to about 250 microns, this deficiency is cured by the teaching of *Ward*, and that although *Trofast* does not teach the order of steps used in preparing the dry powders, this deficiency is cured by the teaching of *Keller*. Applicant respectfully disagrees with the Examiner for reasons set forth below.

Applicant has recognized that in a tertiary inhalation composition comprising two different medicament particles of inhalable sizes and a relatively coarse carrier, the manner of attachment of the two different medicament particles to the carrier affects the properties of the composition. Applicant has also recognized that the manner of attachment of the two different medicaments to the carrier may be varied by the order of mixing. This is simply not disclosed or suggested in the prior art. For example, particles which are first mixed with the carrier would bind directly to the carrier, while particles which are mixed in the subsequent steps may bind directly to medicament particles already deposited on the surface of the carrier. This is especially the case when the amount of the particles that are first mixed with the carrier is sufficiently large that a monolayer is formed on the carrier particles. The claimed method, which involves mixing a portion of the first particulate inhalant medicament in an amount sufficient to form

a monolayer on the carrier, thereby forming a first mixture, then mixing the first mixture with the second particulate inhalant medicament to form a second mixture, and finally mixing the second mixture with the remaining first particulate inhalant medicament, results in a tertiary inhalation composition having desirable properties. Thus, the claimed invention is based on both the recognition of a problem associated with the preparation of a tertiary inhalation composition comprising different medicament particles of inhalable sizes and a coarse carrier, and a successful way of solving this previously unrecognized problem via a specific sequence of mixing the ingredients.

As explained in paragraph [0018] of the present application, it is believed that the formation of a monolayer of the first medicament on the carrier contributes to the production of blends that are highly homogeneous and produce consistently high fine particle fractions of both drugs. These advantages are demonstrated in the Example of the present application. For example, Example 1 beginning on page 10 of the specification discloses the preparation of an exemplary dry powder inhalation composition of the present invention containing budesonide and formoterol as the medicaments and lactose as the carrier. The dry powder inhalation composition was then tested using a multidose dry powder inhaler. The test results demonstrate that the composition gave excellent dose uniformity and reliability for both budesonide and formoterol with a good fine particle fraction for both medicaments (*see*, Tables 3 and 4 on page 12).

Inventions based on solving a previously unknown problem have been held to be non-obvious and patentable. In *Eibel Process Co. v. Minnesota & Ontario Paper Co.*,

261 U.S. 45 (1923), the Supreme Court ruled that the first recognition of the existence of a problem is not obvious and involves discovery and invention. Similarly, in *In re Nomiya*, 509 F.2d 566, 184 USPQ 607 (C.C.P.A. 1975), the Court of Customs and Patent Appeals (CCPA) held that the doctrine established by the Supreme Court in *Eibel Process* also applies when the inventor was the first to encounter or perceive a problem even though he uses known or obvious means of solving it.

The Examiner has determined that the ordinary skilled artisan would have had a reasonable expectation that mixing of the actives in the amounts taught by the references would result in a monolayer coating. However, there is no teaching or suggestion in the cited publications that in a tertiary composition, formation of a monolayer of first medicament particles on the carrier particles would be desirable, or more specifically that a monolayer can be created by first mixing a portion of the first medicament within the particulate carrier (to form a monolayer) followed by mixing in the second medicament, and then a second portion of the first medicament. Thus, there is simply no motivation for the skilled person to provide a monolayer of the first medicament on the carrier particles in a tertiary composition.

The reasoning as to why a person skilled in the art would have combined *Trofast* with *Ward* and *Keller* to arrive at the presently claimed invention is not sustainable. As acknowledged by the Examiner, *Trofast* does not teach or suggest the VMD of the particulate carrier material, or the order of mixing the medicaments and the carrier as recited in the present claims. Nor does *Trofast* teach or suggest that the order of mixing its ingredients is important or affects the properties of the dry powder formulations.

The Office relies upon *Ward* to deal with the issue of particle size of the carrier. However, reliance upon Ward is misplaced in at least two respects. First, *Trofast* and *Keller* are both concerned with the provision of dry powder formulations comprising lactose as a carrier substance (see the examples of both documents). In contrast, *Ward* is directed to dry powder formulations that do not include lactose. Indeed, a key feature of the formulations disclosed in *Ward* is the avoidance of the disadvantages associated with the use of lactose (see the abstract, line 65 of column 2 to line 12 of column 3, and lines 31 to 33 of column 3 of *Ward*). Instead of using "inert" carrier particles, *Ward's* pharmaceutical formulations contain micro fine particles and carrier particles wherein both types of particle are made of an active pharmaceutical compound. Upon inhalation, the active micro fine particles and carrier particles are separated whereupon the micro fine particles travel through the throat and into the lungs and the carrier particles pass into the throat and are swallowed for delivery to the GI tract. *Ward* is not concerned with compositions comprising a first particulate inhalant medicament, a second particulate inhalant medicament, and an inert carrier, as recited in the presently claimed invention.

Second, *Ward's* teaching of the use of relatively larger carrier particles is directly contrary to the teaching in *Trofast* teaches that all ingredients in its formulation, including the carrier such as lactose, are rendered less than 10 μm in size. *See, e.g., Trofast*, column 2, lines 3-10, "[t]he ingredients of the formulation according to the invention *must* both be in a finely divided form, i.e. their mass median diameter should generally be less than 10 μm, preferably from 1

to 7 μm ..." (emphasis added). Plainly, *Trofast* emphasizes the importance of having all the ingredients the same particle size.

The routineer in the art, seeking to modify *Trofast's* formulations, would not have diverged from its teachings and proceeded in a totally opposite direction regarding the nature and size of the carrier particles. Thus, the attempt to establish *prima facie* obviousness based on the combination of *Trofast* and *Ward* could only be arrived at via hindsight reconstruction. The determination of the Office would require the person of ordinary skill to proceed directly contrary to the teachings in *Trofast* in two respects -- by replacing the carrier particles with particles made of an active agent that are much larger in size. These results would be inconsistent with the objectives of both patentees. Prior art publications must be evaluated in their entirety. Thus, it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *See, In re Mercer* 515, F.2d 1161, 1165-66, 185 U.S.P.Q. 774, 778 (C.C.P.A. 1975).

In view of the foregoing, the person of ordinary skill in the art would not have been motivated to modify *Trofast's* formulations in accordance with the teachings in *Ward*.

The Office has cited *Keller* to address the claimed recitations with respect to the order of mixing the ingredients. Here again, *Keller* misses the mark. *Keller* teaches that an active ingredient, an excipient (*i.e.*, magnesium stearate) and a carrier can be mixed in any order. As Applicant has already argued, although *Keller* states that a pharmaceutically inactive

carrier, a pharmaceutically active compound and magnesium stearate can be mixed with one another in any desired sequence, there is no teaching of how two active ingredients and an inactive carrier should be combined. Furthermore, there is no suggestion that one of the active ingredients should be provided in two separate portions. There is certainly no disclosure in *Keller* of a method for producing a dry powder inhalation composition wherein a first particulate inhalant medicament is provided in a first portion in an amount sufficient to create a monolayer on the particulate carrier. If anything, *Keller*'s teachings would have suggested to a person skilled in the art that the order of mixing is not critical and does not influence the properties of the final product.

The Office maintains that although *Trofast* lacks an explicit teaching of the order of steps used in preparing the dry powders, this deficiency is cured by the teaching of *Keller* because *Keller*'s teaching of mixing different ingredients in any desired sequence "encompasses" the claimed step sequences. However, Applicant is unaware of any legal authority or precedent that supports or otherwise endorses the proposition that prior art teachings that encompass a claimed invention necessarily render it obvious. To the contrary, there is ample precedent that such inventions might well be nonobvious and thus patentable over broad or generic prior art teachings. Thus, *Keller* does not cure the deficiency of *Trofast*.

In view of the foregoing, Applicant respectfully submits that claims 1-19 would not have been obvious over *Trofast* in view of *Ward* and *Keller*. Withdrawal of the rejection is respectfully requested.

As it is believed that all of the rejections set forth in the Office Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Patent Office is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

By Weining Wang

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